The Sympathetic System and Hypertension
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Measurement of regional sympathetic activity in lean essential hypertension patients using electrophysiologic (sympathetic nerve recording) and neurochemical (measurement of norepinephrine spillover) techniques demonstrates activation of sympathetic outflow to the heart, kidneys, and skeletal muscle vasculature in younger (< 45 years) patients. The increase in sympathetic activity is a mechanism for both initiating and sustaining the blood pressure elevation. Sympathetic nervous activation also confers specific cardiovascular risk. Stimulation of the sympathetic nerves to the heart promotes the development of left ventricular hypertrophy and contributes to the genesis of ventricular arrhythmias and sudden death. Sympathetically mediated vasoconstriction in skeletal muscle vascular beds reduces the uptake of glucose by muscle, and is thus a basis for insulin resistance and consequent hyperinsulinemia.

Understanding the neural pathophysiology of obesity-related hypertension has been more difficult. In normotensive obesity, renal sympathetic tone is doubled, but cardiac norepinephrine spillover (a measure of sympathetic activity in the heart) is only 50% of normal. In obesity-related hypertension, there is a comparable elevation of renal norepinephrine spillover, but without suppression of cardiac sympathetics, as here cardiac norepinephrine spillover is more than double that of normotensive obese and 25% higher than in healthy volunteers.

Increased renal sympathetic activity in obesity may be a necessary cause for the development of hypertension (predisposing to hypertension development), but apparently is not a sufficient cause. The discriminating feature of the obese who develop hypertension is the absence of the presumably adaptive suppression of cardiac sympathetic outflow seen in the normotensive obese.

The sympathetic nervous system has moved towards center stage in cardiovascular medicine. The importance of sympathetic activation in heart failure progression and mortality and in the generation of ventricular arrhythmias is now well established. In essential hypertension also, although the mechanism differs somewhat between the lean and obese, the sympathetic nervous system is a key factor in the genesis of the disorder, and additionally promotes the development of complications. Through their central inhibition of sympathetic nervous activity, I1 agents such as rilmenidine powerfully reduce sympathetic nervous activity in essential hypertension patients, lowering blood pressure, and carrying the potential for specific cardiovascular protection. Am J Hypertens 2000; 13:99S–105S © 2000 American Journal of Hypertension, Ltd.

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INTRODUCTION

The importance of sympathetic nervous activation in the pathogenesis of human heart failure, ventricular arrhythmias, and essential hypertension has been widely studied, and the therapeutic value of sympathetic nervous inhibition, currently under continuing investigation in these conditions, is already evident. In the medical management of cardiac arrhythmias, there has been a recent major revolution. Many of the drugs previously widely used for the treatment of ventricular tachyarrhythmias, introduced into clinical practice on the basis of effects on isolated cardiac myocyte membrane electrolyte fluxes and membrane potential, were found in the Cardiac Arrhythmia Suppression Trial (CAST) study to substantially increase the risk of sudden death. This has led to greater recognition of both the importance of autonomic nervous mechanisms in arrhythmia development, and the therapeutic value of drugs with antiadrenergic activity as antiarrhythmics. The level of sympathetic nervous drive to the failing heart is a major determinant of prognosis in patients with cardiac failure, a finding that provides neurobiologic evidence justifying the use of antiadrenergic drugs in this condition. The \( \beta \)-adrenergic blocking drug carvedilol, in a recently completed multicenter trial, lowered mortality rates in heart failure by approximately 65\%.

In primary human hypertension, analysis of regional sympathetic nervous system function has demonstrated activation of the sympathetic nervous outflows to the heart, the kidneys, and skeletal muscle vasculature, particularly in younger patients. This sympathetic activation no doubt contributes to blood pressure elevation, but has been suggested to have adverse consequences beyond this, possibly contributing to the development of atherosclerosis, cardiovascular hypertrophy, and cardiac arrhythmias.

Through their inhibition of sympathetic nervous activity, \( I_1 \) binding agents carry the potential for specifically conferring cardiovascular protection in patients with hypertension. In this review, the sympathetic neural pathophysiology of essential hypertension is catalogued, and the justification for the use of central sympathetic inhibition by \( I_1 \) binding agents such as rilmenidine in its treatment is presented.

MEASUREMENT OF SYMPATHETIC NERVOUS FUNCTION IN HUMAN HYPERTENSION

Measurement of the excretion of the sympathetic nervous neurotransmitter norepinephrine in urine is now largely obsolete as a test of human sympathetic nervous activity, whereas assay of the plasma concentration of norepinephrine, still widely used, has two major limitations. The first is that no information is provided on regional sympathetic nervous function; sympathetic nervous system responses typically show regional differentiation that can be detected in clinical research only by techniques that assess organ-specific sympathetic function. The second deficiency is the dependence of plasma norepinephrine concentrations on rates of removal of the neurotransmitter from plasma, not just sympathetic tone and norepinephrine release.

CLINICAL METHODS FOR ASSESSING REGIONAL SYMPATHETIC NERVOUS SYSTEM FUNCTION

Clinical measurements of rates of sympathetic nerve firing and of norepinephrine release to plasma provide the most secure basis for studying regional sympathetic nervous function in patients with hypertension (Figure 1).
Clinical Microneurography This technique provides a method for studying nerve firing rates, in subcutaneous sympathetic nerves distributed to skin and skeletal muscle (Figure 1). The technique involves the insertion of fine tungsten electrodes through the skin, with positioning of the electrode tip in sympathetic fibers of, most commonly, the common peroneal or median nerves. Multifiber recordings of bursts of nerve activity, synchronous with the heart beat, are generated.7

Noradrenaline Spillover Rate Measurements Neurotransmitter release can be studied clinically using radiotracer-derived measurements of the appearance rate of norepinephrine in plasma from individual organs6 (Figure 1). Microneurographic methods do not give access to sympathetic nerves of internal organs, a limitation that is overcome by using regional norepinephrine spillover measurements. With infusion of tritiated norepinephrine and regional blood sampling from the coronary sinus and renal veins, neurotransmitter release from the heart and kidneys can be measured.2,4,6

Heart rate power spectral analysis techniques are commonly applied as an alternative, noninvasive method for studying sympathetic function in the heart. With this technique, mathematical partitioning allows identification of individual, superimposed rhythms producing cyclical variation in heart rate and arterial pressure. The autonomic nervous system provides the principal effector mechanism for heart rate variability. Although the low-frequency heart rate variability (approximately 0.1 Hz) derives in part from the influence of the cardiac sympathetic nerves, it is very misleading when used as a measure of cardiac sympathetic firing.8,9

INCREASED SYMPATHETIC NERVOUS ACTIVITY IN HUMAN HYPERTENSION

Evidence drawn from a number of sources, utilizing both electrophysiologic and neurochemical techniques, provides compelling evidence that overactivity of the sympathetic nervous system is commonly present in younger patients with essential hypertension (Figure 1). In borderline and established hypertension, nerve firing rates in postganglionic sympathetic fibers passing to skeletal muscle blood vessels are increased. There is also increased spillover of the sympathetic neurotransmitter norepinephrine from the heart and kidneys, providing evidence of stimulated sympathetic outflow to these organs.4,5,10,11

The increased cardiac and renal sympathetic nerve firing provides a plausible mechanism for the development of hypertension, through the regulatory influence of the sympathetic nervous system on renin release, glomerular filtration rate, and renal tubular sodium reabsorption, and on cardiac growth and pump performance.

There have been some misgivings that sympathetic nervous activation in hypertension might, perhaps, simply represent an alerting response in the laboratory, additionally contributed to by anxiety resulting from recent diagnostic labeling of patients as hypertensive.12 Unlike in mental stress reactions, however, the sympathetic nervous activation present in essential hypertension spares the sympathetic innervation of the skin5 and hepatomesenteric circulation,13 and is not accompanied by increased adrenal medullary secretion of epinephrine. In a mental stress response, epinephrine secretion is increased and the sympathetic outflow to skeletal muscle vasculature typically is unchanged or reduced, whereas that to skin is increased, and hepatomesenteric sympathetic tone is increased.6,14,15

CAUSES OF INCREASED SYMPATHETIC ACTIVITY IN ESSENTIAL HYPERTENSION

The specific causes of the increased sympathetic activity in essential hypertension remain largely unknown, although genetic influences are evident and behavioral and lifestyle factors appear to be involved.

Genetics The heritability of sympathetic overactivity in primary human hypertension has been little studied. The limited search undertaken so far for single gene abnormalities involving the sympathetic nervous system has been unsuccessful in patients with high blood pressure. Sympathetic nervous activity does appear to be heritable in healthy subjects with normal blood pressure. In monozygotic twins,16 skeletal muscle sympathetic nerve firing rates were found to be almost identical in individual pairs, unlike in randomly paired groupings of unrelated subjects in whom a wide range of nerve firing rates was evident. Similarly, twin studies investigating the heritability of plasma norepinephrine concentrations have attributed approximately 50% of the variance to genetic factors.17 Normotensive young men with a family history of hypertension do have higher rates of norepinephrine spillover to plasma than young men with a negative family history of hypertension.18

Lifestyle Influences on Blood Pressure Stress and Behavior Continuing uncertainty exists concerning the role of stress in the sympathetic activation of hypertensive patients and in the pathogenesis of human hypertension in general. Though studies substantiating a role for experimental stress in causing hypertension in laboratory animals are interesting and important, it is another matter to demonstrate that essential hypertension is due to psychosocial conflict. Clinical, epidemiologic, and laboratory research does, however, provide increasingly strong support for the no-
tion that behavioral and psychologic factors are of importance in the pathogenesis of human hypertension. Of particular importance in this regard are epidemiologically based observations made on human populations, which demonstrate blood pressure elevation soon after migration, and long-term follow-up studies of human populations, such as cloistered nuns, living in secluded and unchanging environments, in whom blood pressure does not show the expected rise with age.

Although the concept that in some patients essential hypertension may arise by psychosomatic mechanisms is not entirely unproven, there is a substantial body of supporting experimental and clinical evidence. Long-term neural effects of stress on renal function is a probable mediating mechanism in blood pressure elevation.

Obesity and Increased Dietary Energy Intake Patients with primary hypertension are commonly overweight. Because positive energy balance initiates thermogenesis by stimulation of the sympathetic nervous system, the sympathetic activation seen in essential hypertension could perhaps represent an adaptive response to overeating, a hypothesis proposed by Landsberg. An excessive dietary energy load is known to stimulate the sympathetic nervous system and elevate arterial pressure. Calorie restriction reduces both sympathetic activity and blood pressure.

There is selective activation of the sympathetic nerves to the kidneys and skeletal muscle vasculature in normotensive human obesity, but suppression of the cardiac sympathetic outflow (Figure 2). The possible importance of activation of the renal sympathetic outflow in the pathogenesis of obesity-related hypertension is illustrated in a recent study on dogs made obese by overfeeding, where renal denervation prevented the development of hypertension. In obesity-related hypertension, there is a comparable elevation of renal norepinephrine spillover, but without suppression of cardiac sympathetics, as here cardiac norepinephrine spillover is more than double that of normotensive obese and 25% higher than in healthy volunteers (Figure 2). Increased renal sympathetic activity in obesity may be a necessary cause for the development of hypertension (and predisposes to hypertension development), but apparently is not a sufficient cause. The discriminating feature of the obese who develop hypertension is absence of the adaptive suppression of cardiac sympathetic outflow seen in the normotensive obese.

Physical Inactivity An additional factor possibly contributing to sympathetic nervous overactivity in hypertensive patients is sedentary lifestyle. Regularly performed physical exercise produces long-term lowering of blood pressure. The blood-pressure-lower-
anism of peripheral sympathetic activation with stress, obesity, and physical inactivity. Catecholaminergic neurons, releasing norepinephrine are widely distributed in the brain, but are located in particular in the medulla and pons. The hypothalamus, and parts of the limbic system including the amygdala, receive projections from these brainstem noradrenergic nuclei. Electrophysiologic and anatomical experiments carried out in animals provide evidence of a connection between pressor noradrenergic hypothalamic and brainstem centers and sympathetic preganglionic neurons in the thoracolumbar cord.

CNS Monoamine Neural Control of Sympathetic Nervous Activity in Healthy Humans Brain norepinephrine turnover can be estimated clinically by measuring the overflow of norepinephrine and its lipophilic metabolites into the internal jugular veins. CNS norepinephrine turnover can be estimated from the combined overflow of norepinephrine and its lipophilic metabolites, dihydroxyphenylglycol (DHPG) and 3-methoxy-4-hydroxyphenylglycol (MHPG). In resting healthy human subjects, the turnover of norepinephrine in subcortical brain regions (with the internal jugular vein, which predominantly drains subcortical brain regions being identified using a cerebral venous sinus scan) correlates directly with muscle sympathetic nerve firing rates measured by microneurography.

CNS Norepinephrine Turnover in Essential Hypertension In hypertensive patients, norepinephrine spillover from the brain on average is higher than in healthy subjects, as is the overflow into the internal jugular veins of the lipophilic metabolites of norepinephrine, DHPG, and MHPG. In patients with an increased spillover of norepinephrine and its metabolites from the brain, peripheral sympathetic activity is increased. Cerebral venous sinus scans indicate that the increased overflow of norepinephrine, DHPG, and MHPG in hypertensive patients is from subcortical brain regions only. Although the exact regional topography of the excitation of brain noradrenergic neurons in essential hypertension is not known, and the precise neurophysiologic basis of the sympathetic nervous system stimulation present in patients with essential hypertension remains unclear, these recent findings do suggest a primary importance in pathogenesis of increased neuronal firing in forebrain noradrenergic pressor areas.

A Possible Relation of Sympathetic Nervous Overactivity to the Clinical Consequences of Hypertension? Whereas the sympathetic activation present in human hypertension no doubt contributes to the blood pressure elevation, it seems to have additional adverse consequences in hypertensive patients, which go beyond this. Neural vasoconstriction can have undesirable metabolic effects, in skeletal muscle impairing glucose delivery to muscle, causing insulin resistance, and hyperinsulinemia, and, in liver, retarding postprandial clearing of lipids, contributing to hyperlipidemia.

Similarly, high sympathetic nervous activity in the heart of hypertensive patients may be deleterious. The importance of neural mechanisms in arrhythmogenesis is well established, with stimulation of the cardiac sympathetic outflow predisposing to ventricular tachycardia and ventricular fibrillation in a variety of experimental models of arrhythmia development. Increased cardiac sympathetic nerve firing, as measured by cardiac norepinephrine spillover, has also been demonstrated to commonly underlie clinical ventricular tachyarrhythmias. A comparable proarrhythmic effect is probable in hypertension also. However, in hypertensive patients, the relative contributions of left ventricular hypertrophy—which promotes reentrant arrhythmias—increased cardiac sympathetic activity, and coronary atherosclerosis to the arrhythmia development to which these patients are prone are uncertain at this stage. A trophic effect of sympathetic activation in the human heart is probable in hypertensive patients, perhaps contributing to the development of left ventricular hypertrophy. A growth-promoting effect of norepinephrine on cardiac myocytes has been demonstrated in vitro.

Effects of Antihypertensive Drugs on Sympathetic Nervous Function: A Special Place for Drugs Inhibiting the Sympathetic Nervous System? Changes commonly occur in sympathetic nervous system function during drug treatment of hypertension, representing in some cases therapeutic sympathetic inhibition by the drug, and in others reflex adaptations opposing a drug’s efficacy. Examples of the former are the reduction in sympathetic nerve firing with I1 binding agents, and of the latter, the reflex sympathetic activation produced by some slow channel calcium influx blockers. As sympathetic nervous system activation in patients with essential hypertension might have adverse effects, it is pertinent to ask whether additional stimulation of the sympathetic nervous system by antihypertensive drugs is undesirable, and conversely, whether specific inhibition of the sympathetic nervous activation commonly present in hypertensive patients is beneficial. This issue has been brought into recent focus by claims, hotly contested, that vasoactive calcium channel blockers may be harmful, in rapid-release pharmaceutical formulations, and perhaps increase cardiac risk by stimulating sympathetic activity in the heart.

The Rationale of Central Pharmacologic Inhibition of the Sympathetic Nervous System in Hypertension
Given that sympathetic activation in hypertensive patients is centrally mediated, and probably contributes to unwanted cardiac effects, might it be appropriate to specifically recommend drugs inhibiting the sympathetic nervous system outflow in patients with human hypertension in whom sympathetic nervous activation is present? One aim of antihypertensive drug therapy has been to use drugs whose mechanism of action is closely linked to the underlying pathophysiology of human hypertension. The expectation is that this will lead to greater efficacy in reducing clinical cardiovascular complications of hypertension, with a lesser incidence of adverse drug effects. Tailoring of antihypertensive therapy to pathophysiology, however well based logically, given our present state of knowledge cannot be the primary therapeutic principle in hypertension care. Overriding clinical considerations commonly apply in the choice of initial therapy, including the presence of coexisting illnesses carrying particular pharmaceutical recommendations (such as the avoidance of β-adrenergic blockers in asthmatics, or their use with coexisting angina), the potential surgical cure of a secondary hypertension, safety for the fetus in pregnancy hypertension, and the intolerance of elderly patients for postural hypotension in the face of inhibition of neurocirculatory reflexes. This point being made, the important and actively researched—but to date incompletely answered—question remains: of all antihypertensive drugs, do those inhibiting the sympathetic nervous system best reduce cardiovascular risk?

REFERENCES


